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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/460,186	06/02/1995	REID VON BORSTEL	1331-138	5103

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EXAMINER	
OWENS JR, HOWARD V	
ART UNIT	**PAPER NUMBER**
1623	29

DATE MAILED: 02/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/460,186	VON BORSTEL ET AL.	
	Examiner	Art Unit	
	Howard V Owens	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2002*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Reply to Board of Appeals Remand

The following is a reply to applicant in accordance with the Board of Appeals comments filed 4-30-2002, regarding the Appeal Brief of 7-31-01.

Initially it should be noted that the Board reserved it's comments to a "Final Office Action"; however, the grounds of rejection as set forth in the examiner's answer mailed 7-31-01, was based on paper no. 5, which was recited in the examiner's answer. The examiner's answer did not indicate that the grounds of rejection was based on a final office action or final rejection. There is no indication that the board substantively reviewed the cited and proper grounds of rejection as set forth on pp. 4 and 6 of the examiner's answer. The board has continually noted that the grounds of rejection can not be based on multiple papers or actions and evinces this as a grounds for remanding applications to the examiner.

From MPEP §1208:

"(A) Examiners may incorporate in the answer their statement of the grounds of rejection merely by reference to the final rejection (or a single other action on which it is based, MPEP § 706.07). Only those statements of grounds of rejection appearing in a single prior action may be incorporated by reference. An examiner 's answer should not refer, either directly or indirectly, to more than one prior Office action."

Thus substantive review of the grounds of rejection as set forth in paper no. 5 should have been afforded since the examiner did not reference multiple actions, i.e. a final office action and paper no. 5 as the grounds of rejection. The examiner's answer clearly sets forth on pp. 4 and 6 that the grounds were based on the action from paper no. 5 which clearly set forth the motivation for one of skill in the art to arrive at the claimed

invention and addressed each claim element. Applicant based it's appeal brief on the final rejection; however, there is no requirement that the examiner's grounds of rejection be limited to the final rejection.

Kralovansky and Kelsen references

It is noted that Kralovansky and Kelsen et al. were relied upon in the response to final rejection and the Appeal Brief of record; copies of these references were never submitted to the PTO accompanied by a 1449 prior to remand to the examiner. Although applicant notes that Kralovansky was "already of record" a copy of this reference has not been submitted to the PTO to date. Although Kelsen will be considered, it is noted that a copy of Kelsen was filed after the remand to the examiner. If applicant desires consideration of the Kralovansky reference, a copy of the reference with an accompanying IDS should be submitted.

Kelsen et al., post dating applicant's filing, was submitted purportedly to show that the unexpected result of reduced gastrointestinal damage was found through administering acylated uridine after administration of a high dose of 5-fluorouracil (5-FU). This reference supports the motivation set forth throughout prosecution by the examiner that the motivation to use an acylated nucleoside as set forth in the prior art resides in the increase of serum/tissue levels of uridine. Kelsen states that "uridine can ameliorate 5-FU toxicity by competing with FU anabolites..", moreover, that oral uridine is poorly absorbed and that the use of a high dose of uridine is technically cumbersome. Given this recognition it is clear that one of skill in the art presented with the prior art of Von Borstel, wherein it is taught that you can achieve elevated levels of uridine via administration of acylated uridine, would be motivated to use an acylated uridine over a non-acylated uridine.

Supplemental Reply Brief/Calabresi reference

A copy of the Calabresi reference has not been properly submitted to the examiner with an accompanying 1449 for review with this application.

It should also be noted that applicant's submission of the supplemental reply brief filed 11-30-01 was not entered nor commented on in the examiner's answer because submission of a supplemental reply brief is improper, per MPEP §1210:

"(C) After the examiner has notified the appellant by written communication that the reply brief has been entered and considered and that the application will be forwarded to the Board (for example, by mailing a PTOL-90 with form paragraph 12.47, as described in MPEP § 1208.03).

Any amendment, affidavit, or other paper relating to the appeal, filed thereafter but prior to the decision of the Board, may be considered by the examiner only in the event the case is remanded by the Board for that purpose.

Obviousness Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 5,968,914 ('914). Although the conflicting claims are not identical, they are not patentably distinct from each other because both are drawn to a method of treating toxicity due to a pyrimidine nucleoside analog comprising administration of an acyl derivative of a non-methylated pyrimidine nucleoside. The instant claims do not set forth the condition targeted for treatment with the pyrimidine nucleoside; wherein '914 sets forth the targeted condition as cancer. However, the scope of the instant claims generically includes the uses associated with the pyrimidine nucleoside, thus recitation of uses of the pyrimidine nucleoside as set forth in the species of either cancer or viruses would be obvious to one of skill in the art. It would have been *prima facie* obvious to use a acyl derivative of a non-methylated pyrimidine nucleoside with a pyrimidine nucleoside. One of skill in the art would have been motivated to use an acyl derivative with a pyrimidine nucleoside because the scope of treatment is the toxicity associated with the pyrimidine nucleoside. Regardless of the targeted disease, the use of the pyrimidine nucleoside is established in the art; therefore, the use of the acyl derivative with the pyrimidine nucleoside is to reduce the toxicity when ever the pyrimidine nucleoside is used as the primary active agent.

Claims 1-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48-74 of copending Application No. 08/473,332 ('332). Although the conflicting claims are not identical, they are not patentably distinct from each other because both are drawn to a administering a pyrimidine nucleoside analog with an acyl derivative of a non-methylated pyrimidine nucleoside. The instant claims do not set forth the condition targeted for treatment with the pyrimidine nucleoside; wherein '332 sets forth the

targeted condition as a viral infection. However, the scope of the instant claims includes the uses generically associated with the pyrimidine nucleoside, thus recitation of uses of the pyrimidine nucleoside as set forth in the species of either cancer or viruses would be obvious to one of skill in the art. It would have been *prima facie* obvious to use a acyl derivative of a non-methylated pyrimidine nucleoside with a pyrimidine nucleoside. One of skill in the art would have been motivated to use an acyl derivative with a pyrimidine nucleoside because the scope of treatment is the toxicity associated with the pyrimidine nucleoside. Regardless of the targeted disease, the use of the pyrimidine nucleoside is established in the art; therefore, the use of the acyl derivative with the pyrimidine nucleoside is to reduce the toxicity when ever the pyrimidine nucleoside is used as the primary active agent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

35 U.S.C. 103 rejection

The rejection of claims 1-25 under 35 U.S.C. 103 is maintained for the reasons of record set forth below.

Claims 1-15, 18, 19, 22-25 are rejected under 35 U.S.C. 103. This rejection is set forth in prior Office action, Paper No. 5 and recited below.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the

subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1 - 15, 18 - 19, and 22 - 25 are rejected under 35 U.S.C. 103 as being unpatentable over Martin et al. (Cancer Res., 1982) or Sommadossi et al. (Antimicrobial Agents and Chemotherapy, 1988) view of Von Borstel et al. (WO 89/03837) and Falcone et al. (Blood, 1990).

The claims are directed to a method for treating cancer comprising administering a pyrimidine nucleoside analog and acylated uridine, deoxyuridine, cytidine or deoxycytidine.

Claims 18 and 19 include a uridine phosphorylase as an additional component.

Martin et al. teaches that administering exogenous uridine can reduce the toxicity of 5-FU and actually "rescue" mice from a toxic dose of 5-FU. Sommadossi et al. also teaches that uridine administration can reduce the toxicity of a pyrimidine nucleoside analog, AZT. Neither Martin et al. nor Sommadossi et al. teaches the use of acylated uridine or cytidine.

Von Borstel et al. bridges the nexus between the prior art and the invention as claimed as it teaches a method for elevating the serum and tissue levels of free uridine or cytidine comprising administering the acylated prodrugs thereof (see pp. 7 –12 and claims 10 - 15). Von Borstel teaches that the acylated derivatives may be administered parentally or orally and that the derivatives have "no untoward pharmaceutical effects (p. 7, line 8)". Von Borstel further teaches that the derivatives improve the bioavailability of cytidine and uridine by enhancing the transport of those nucleosides across the gastrointestinal tract, the blood brain barrier and other biological membranes with the added benefit that they are resistant to catabolism by nucleoside deaminases and nucleoside phosphorylases in the intestine, liver, other organs and the bloodstream (p. 9, lines 11-17). It would have been *prima facie* obvious to the person of ordinary skill in the art at the time of the invention to have substituted acylated uridine or cytidine as taught by Von Borstel et al. in place of the free uridine taught by Martin et al. and Sommadossi et al. One of skill in the art would have been motivated to substitute an

acyl derivative in order to increase the serum and tissue levels of uridine and therefore, reduce the toxicity of 5-FU or AZT or any other pyrimidine nucleoside analog, regardless of the chemotherapeutic target of said nucleoside analog.

Neither Martin or Sommadossi nor Von Borstel teaches the use of an inhibitor of uridine nucleoside phosphorylase as a way to increase serum and tissue levels of free uridine. However, Falcone et al. does teach the use of an inhibitor of uridine nucleoside phosphorylase, benzylacyclouridine, to increase the serum and tissue levels of free uridine, and thereby reducing the toxicity of AZT. Therefore, a method of using either acylated U or C in combination with a uridine phosphorylase inhibitor would also have been obvious to the person or ordinary skill in the art at the time of the invention wanting to obtain the combined uridine elevating effects of two compounds known in the art to increase the bioavailability of free uridine.

Claims 16 and 17 are rejected under 35 U.S.C. 103. This rejection is set forth in prior Office action, Paper No. 5 and recited below.

Claims 16 - 17 and 20 - 21 are rejected under 35 U.S.C. 103 as being unpatentable over Bhalla et al. (Blood, 1987) in view of Von Borstel et al. (WO 89/03838) and Hanze et al. (4,017,606).

Claims 16 - 17 are directed to a method for preventing or treating toxicity due to pyrimidine nucleoside analogs comprising the administration of a pyrimidine nucleoside analog and an acylated deoxycytidine. Claims 20 - 21 further include a cytidine deaminase inhibitor.

Bhalla et al. teaches that the administration of deoxy-cytidine reduces the toxicity of cytosine arabinoside. Bhalla does not teach the use of acylated deoxycytidine in place of free deoxycytidine. However, Von Borstel et al. does teach the use of acylated deoxycytidine in place of free deoxycytidine in order to obtain higher serum and tissue levels of deoxy-cytidine (see claim 32). It would have been *prima facie* obvious to the person of ordinary skill in the art at the time of the invention to have substituted acylated deoxycytidine as taught by Von Borstel et al. for deoxycytidine as taught be Bhalla et al. One of skill in the art would have been motivated to substitute an acylated derivative for a non-acylated derivative for the purpose of increasing the serum and tissue levels of

free deoxycytidine, thus reducing further the toxicity of cytosine arabinoside or other pyrimidine nucleoside analogs.

Neither Bhalla nor Von Borstel disclose a cytidine deaminase inhibitor. However, Hanze et al. does disclose tetrahydrouridine as a cytidine deaminase inhibitor (column 5, lines 42 - 61) and its use to prevent the degradation of a cytidine nucleoside analog. It would have been *prima facie* obvious to the person of ordinary skill in the art at the time of the invention to have replaced free deoxycytidine with a combination of acylated deoxycytidine and tetrahydrouridine. One of skill in the art would have been motivated to combine an acylated deoxycytidine and tetrahydrouridine in order to obtain even higher levels of free cytidine in serum and tissue which would create even more reduction in the toxicity of cytidine arabinose or any other pyrimidine nucleoside analog.

Unexpected Results

Applicant argues that unexpected results are presented on pp. 42-44 and Example 6 of the specification. However, pp. 42-44, contain conclusory statements about the compounds of the invention with no factual evidence to evince an unexpected result, "An applicant cannot prove unexpected results with attorney argument and bare statements without objective evidentiary support", *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342, quoting, *In re Lindner*, 457 F.2d 506, 508, 59 C.C.P.A. 920 (CCPA 1972); *In re Geisler*, 116 F.3d 1465 (Fed. Cir. 1997) ("attorney argument [is] not the kind of factual evidence that is required to rebut a prima facie case of obviousness"); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) ("It is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements . . . [do] not suffice." (quoting *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984)).

Example 6, doesn't present a result not contemplated by the prior art; moreover, the factual evidence set forth is not commensurate with the scope of the claims. Example 6 concludes that acylated uridine reduces the toxicity associated with 5-FU administration versus nonacylated uridine; the data is actually consistent with the examiner's motivation because example 6, shows that uridine administered intraperitoneally (i.p.) is

actually more effective than TAU administered orally for reducing 5-FU toxicity. Clearly the presence/increase of uridine within the serum/tissues as enhanced by i.p. administration over oral administration is consistent with the prior art's increase in uridine in the serum/tissue via administration of TAU or an acylated form.

"It is well established that the objective evidence of nonobviousness must be commensurate in scope with the claims", *In re Linder*, 59 C.C.P.A. 920, 923, quoting, e.g., *In re Hyson*, 59 CCPA 782, 453 F.2d 764, 172 USPQ 399 (1972); *In re Tiffin*, 58 CCPA 1420, 448 F.2d 791, 171 USPQ 294 (1971). The scope of the claims is not limited to a particular form of administration; thus applicant's contention that there is an unexpected result based on data from oral administration solely is not consistent with the scope of the claims. The results of example 6 are set forth in table 13, wherein it is shown that TAU administered orally was more effective than orally administered uridine at reducing mortality; however, TAU was not as effective as uridine administered i.p. There is no comparison in table 13 of the efficacy of TAU administered i.p. versus uridine i.p. Thus the scope of the claims includes all forms of administration for which applicant claims an unexpected result; wherein there is no commensurate factual data to support this.

More importantly, as cited supra, the prior art of Von Borstel had already recognized that the acylated derivatives of cytidine or uridine had the added benefit over non-acylated derivatives during oral administration in that they are resistant to catabolism by nucleoside deaminases and nucleoside phosphorylases in the intestine, liver, other organs and the bloodstream (p. 9, lines 11-17). Clearly compounds that are more resistant to catabolism through the digestive tract would be more efficacious over those that are not, thus any data demonstrating that the non-acylated uridine was less efficacious was predicted by the prior art and provides a reasonable expectation of success in the use of an acylated derivative over a non-acylated derivative.

For the reasons cited above the rejection of record is maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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